Spontaneous Recurrence of Methamphetamine-Induced Paranoid-Hallucinatory States in Female Subjects: Susceptibility to Psychotic States and Implications for Relapse of Schizophrenia

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Original Paper

In this study, we examined the relationship between increased sensitivity to stress associated with noradrenergic hyperactivity and dopaminergic changes, and susceptibility to subsequent spontaneous recurrences of methamphetamine (MAP) psychosis (i.e., flashbacks). The subjects were 81 physically healthy females. Plasma monoamine metabolite levels were assayed in: 19 flashbackers, of whom 11 experienced a single flashback and 8 exhibited subsequent flashbacks; 20 non-flashbackers with a history of MAP psychosis; 8 subjects with persistent MAP psychosis; and 23 MAP users and 11 non-user controls. All 19 flashbackers had undergone frightening and stressful experiences during previous MAP use. Mild psychosocial stressors then triggered their flashbacks. During flashbacks, plasma norepinephrine levels increased, with a small increase in plasma levels of 3-methoxytyramine, which is an index of dopamine release. Among the 19 flashbackers, the 8 with subsequent episodes had increased NE levels and slightly increased 3-methoxytyramine levels, while the 11 with a single episode displayed small increases in norepinephrine and 3-methoxytyramine levels. Thus, noradrenergic hyperactivity and increased dopamine release in response to mild psychosocial stressors may be responsible for the development of flashbacks. Robust noradrenergic hyperactivity with slightly increased DA release in response to mild stress may induce susceptibility to subsequent flashbacks. Flashbacks and schizophrenia may share the pathophysiology of susceptibility to recurrence of paranoid-hallucinatory states such as stress sensitization, and also noradrenergic hyperactivity and enhanced DA release. Thus, flashbacks may provide an appropriate model of susceptibility to paranoid-hallucinatory states of schizophrenia. The model psychosis is a potential tool for validating basic neurobiological concepts thought to be related to the schizophrenia. A better understanding of the neurobiological mechanisms of susceptibility to recurrence could provide useful information in the development of strategies for preventing relapse.

Introduction

Amphetamines (AMPs) or methamphetamines (MAPs) are primarily taken illicitly to enhance the mood. A severe consequence of AMPs or MAPs abuse is paranoid-hallucinatory states that are often clinically indistinguishable from schizophrenia (especially paranoid type) in non-schizophrenic subjects, occurring in a setting of clear consciousness [5,40]. Individuals with a history of MAP psychosis tend to experience spontaneous recurrence of MAP psychosis (that is, flashbacks) when under stress [39]. We have reported that increased sensitivity to stress associated with noradrenergic hyperactivity, to which dopaminergic chang-

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es may contribute, may be important in the development of flashbacks [53 – 55]. AMPs have been shown to induce enduring sensitization to stress via dopaminergic changes, possibly related to the enduring hypersensitivity to psychotogenic effects of stress found in spontaneous recurrences of AMP psychosis [37]. According to extensive animal studies, prior exposure to stressful stimuli results in noradrenergic hyperreactivity to subsequent mild stress, which in turn may be a precipitating factor in stress-related psychiatric disorders [19,34]. Stress-induced increases in noradrenergic function have been implicated in the recall of traumatic events in posttraumatic stress disorder (PTSD) [41]. Taking these considerations as a whole, noradrenergic hyperactivity with dopaminergic changes in response to mild stress is predicted as critical to the development of flashbacks due to a previous MAP psychosis.

Subjects with flashbacks had either a single flashback episode or further recurrences. More psychosocial stressors may be involved in the first episode of major affective disorders than in subsequent episodes, so that the later episodes imply an increasing susceptibility to recurrence [35]. We therefore expect that stress reactivity associated with noradrenergic hyperactivity and dopaminergic changes may differ in the first flashback episode between an initial episode and subsequent flashbacks.

It is documented that chronic AMP effects overlap with schizophrenia (especially paranoid-type) in their pathophysiology [24]. As with flashbacks, schizophrenic symptoms such as paranoid-hallucinatory states are often relapsed by psychological stressors [23,25]. Progressive neurochemical sensitization [25] or endogenous sensitization [23] to stressful experiences could therefore underlie the onset and deteriorative phases of schizophrenia. So, it is possible that spontaneous recurrences of MAP-induced paranoid-hallucinatory states share the same level of susceptibility as paranoid-hallucinatory states of schizophrenia. Consequently, flashbacks may be an appropriate human model of susceptibility to paranoid-hallucinatory states in schizophrenia.

To examine these possibilities, our first aim was to elucidate the role of dopaminergic changes in addition to noradrenergic hyperactivity in the development of flashbacks, and secondly, to determine susceptibility to subsequent paranoid-hallucinatory flashback episodes. Accordingly, we examined the nature of increased sensitivity to stress associated with noradrenergic hyperactivity and dopaminergic changes during the first episode of flashbacks in subjects with only a single flashback episode and in subjects with subsequent flashbacks. In this study, we addressed whether spontaneous recurrences of MAP psychosis provide an appropriate human model of susceptibility to paranoid-hallucinatory states in schizophrenia.

Methods

Subjects

The subjects were 81 physically healthy females, 39 of whom had previously experienced MAP psychosis; 8 had persistent MAP psychosis, and 34 were normal controls (23 MAP users and 11 non-users, none of whom had experienced MAP psychosis or flashbacks). All were recruited from inmates at a women's prison in the order of admission to the prison. The subject subgroups were age-matched (between single pairs of the subject subgroups, Z or Zc-0.06 – 1.83, $p < 0.07 – 0.94$). All subjects were deemed physically healthy based on physical and neurological examinations and on biochemical screening. None had abused other substances or experienced any psychiatric disorder in the absence of MAP use. Subjects had been tested for other substances by the police and all results were negative. Of the 39 subjects with a history of MAP psychosis, 19 experienced flashbacks during their 15 – 20 months of incarceration ("flashbackers") and the other 20 subjects did not ("non-flashbackers"). The 19 flashbackers were selected on the basis that their plasma monoamine metabolite levels were assayed during the first flashback episode and again within 30 days of the first episode passing. Of these, 11 experienced a single flashback episode without further recurrence, while the others experienced subsequent episodes (two flashbacks per subject). Because MAP psychosis in the 19 flashbackers had disappeared within 730 days before blood collection (mean ± SD, 218.9 ± 216.8 days), the 20 non-flashbackers were selected by adjustment of the time of disappearance of MAP psychosis (273.0 ± 216.4 days). The 8 subjects with persistent MAP psychosis, which had persisted for at least 6 months (17.6 ± 10.5 months) prior to blood collection, were included for comparison with the 19 flashbackers (spontaneous vs. persistent recurrence) to examine the relationship between prior exposure to stressful experiences and plasma monoamine metabolite levels. Our previous studies have involved 10 or 12 [53 – 55] of the 19 flashbackers, 15 of the 20 non-flashbackers, 18 of the 23 user controls, 8 of the 11 non-user controls [55] and 4 [53] or 6 [54,55] of the 8 subjects with persistent MAP psychosis. All subjects were informed that they were free not to take part in the study and could withdraw without penalty. They freely gave written informed consent prior to the study, which was approved by the Medical Care and Classification Division of the Ministry of Justice. Clinical diagnosis was confirmed using the DSM-IV criteria for AMP-induced psychotic disorder. Subjects were further screened using the Structured Clinical Interview for DSM-IV checklist to exclude those with schizophrenia, brief psychotic disorders, delusional disorder, anxiety disorders and PTSD. Flashbacks due to previous MAP psychosis are defined with reference to a general definition of psychedelic drug flashbacks [27] and DSM-IV criteria for hallucinogen persisting perceptions disorder (flashbacks) as a spontaneous recurrence of MAP-induced paranoid-hallucinatory states after a period of normalcy, during which the pharmacological effects of MAP had worn off.

Of the 19 flashbackers, 6 complained of paranoid-hallucinatory flashback states before blood collection and were accordingly treated with haloperidol (1 – 6 mg/day), chlorpromazine (25 – 75 mg/day) or thioridazine (25 – 50 mg/day) for at least 4 weeks before and during the study (medicated flashbackers). The other 13 flashbackers were unmedicated for at least 3 months prior to blood collection. However, they received the neuroleptic treatment just specified above following blood collection during flashbacks due to flashback aggravation (later-medicated flashbackers). The defining characteristics did not differ between the two subgroups. The 20 non-flashbackers were unmedicated for at least 3 months before and during the study since they had no psychiatric symptoms. All subjects were free of other medications.

Stressful experiences

Details of the pattern of MAP use, stressful experiences, and symptoms of MAP psychosis during previous MAP use were obtained from structured interviews and from inmate record reviews. The interviews were conducted by two psychiatrists who were unaware of the subject subgroups before the occurrence of flashbacks upon admission to the prison. Questions addressed specific topics including whether the subjects had had stressful experiences, what stressful experiences had occurred during previous MAP use, and what behavior the subjects had displayed. Stress is usually defined as a physical or psychological factor that poses a threat to the well-being of the subjects, producing a defensive response [22]. Accordingly, the criteria for stressful events during previous MAP use were based on whether the subjects had been overwhelmingly distressed, whether the events met the DSM-III-R criteria for a severe to catastrophic type of psychosocial stressor (axis IV scores of 4 to 6), and whether the subjects had escaped from the situations (defensive response). The criteria for MAP-induced fear-related paranoid-hallucinatory states (perception of threat) during previous MAP use were based on whether the subjects had been overwhelmingly threatened and whether they had taken refuge near or in their houses out of fear (defensive response). Information on the factors triggering flashbacks was obtained from structured interviews and reports made by prison staff. All data were verified through follow-up interviews. Psychosocial stressors, including stressful events and factors triggering flashbacks, were assessed using the Severity of Psychosocial Stressors Scale (axis IV) from the DSM-III-R. When more than one stressor was present, the rating chosen was that of the most severe stressor. To assess anxiety levels related to stress, the State Anxiety Inventory (STAI) was used [42]. STAI data were available for random subsamples of 11 of the 19 flashbackers at two time points (when the flashbacks occurred and at remission) or at a single time point (admission to the prison) for random subsamples consisting of 10 of the 20 non-flashbackers, 9 of the 23 user controls, and 8 of the 11 non-user controls. Blood pressure and heart rate were measured at the time of blood sampling.

Checking for secret MAP use

In Japan, all prisoners, including our subjects, in detention houses and prisons are rigorously prevented from taking MAP or other substances. Incarceration involves repeated searches in accordance with the Cannabis Control Law, Narcotics Control Law and Stimulant Drug Control Law. The prison staff thoroughly searches prisoners' belongings and clothes also and look under the mats in their living quarters. All prisoners are prevented from meeting any visitor other than family members or from receiving sealed correspondence. The Ministry of Justice confirmed that no MAPs or other substances are used secretly in detention houses or prisons [31]. Our subjects expected to be searched by methods authorized under the Prison Law, so they were not frightened by the searches. Venous plasma was tested for MAP in a randomly selected subsample consisting of 9 of the 19 flashbackers at the time the flashbacks occurred using gas chromatography/mass spectrometry as described previously [53]. All analyses were negative.

Plasma monoamine metabolite levels

All subjects were given a low-monoamine, alcohol-free, caffeine-restricted diet for at least 3 months before and during the study while confined in detention houses and in the prison. Blood was obtained from the 19 flashbackers during the prominent paranoid-hallucinatory flashback state of the first flashback episode, which occurred 2 – 14 days after the occurrence of flashbacks, and again 14 to 30 days after cessation of the flashback. The other subjects had a single blood sample assayed when they were transferred to the prison after at least 3 months of confinement in detention houses under similar conditions to the prison. Blood was collected by venipuncture from 10:30 a.m. to 12 noon. Excessive motor activity was not allowed in the prison. Subjects were supine for 20 minutes before and during blood sampling. Plasma was stored at -80°C until assay. Norepinephrine (NE) and its metabolite normetanephrine (NM), epinephrine (E), and dopamine (DA) and its metabolites 3-methoxytyramine (3-MT) and dihydroxyphenylacetic acid (DOPAC) were assayed for using high-performance liquid chromatography with an electrochemical detector as described previously [53]. Sensitivity was 0.01 pmol/ml, except for NM, which was 0.05 pmol/ml. Intraassay and interassay coefficients of variation averaged 10.0 % and 21.1 %, respectively.

Data analysis

Distribution of plasma monoamine metabolite levels were often extremely skewed. The number of observations in this study was small (not exceeding 1,000). Thus, it is appropriate to apply the square-root transformation to reduce the skew and then use a parametric *t*-test [28]. The square-root transformed data were analyzed by one-way analysis of variance (ANOVA) followed by the *post hoc* test (Fisher's Protected Least Significant Difference), the multiple *t*-test. To confirm significant differences in monoamine metabolite levels between flashbacks and remission, and absence of any significant effect of our neuroleptic treatment on monoamine metabolite levels, the transformed values from the 19 flashbackers were analyzed using repeated-measures ANOVA with the presence or absence of neuroleptic treatment as the between subject factor, and presence or absence of flashbacks as the within subject repeated factor [15]. Comparison between subject subgroups was performed using the Kruskal-Wallis test followed by the Mann-Whitney U-test, and the Chi^2 test.

Results

Clinical characteristics of the flashbackers

In Japan, violators of the Stimulant Drug Control Law, including our subjects, are usually sentenced to up to 2 years in prison in a public court. All subjects except for the 11 non-user controls, who had been imprisoned for theft (n = 8), arson (n = 1) and involuntary manslaughter (n = 2), had averaged 1 – 10 intravenous injections of MAP (30 – 60 mg per injection) per day during periods of abuse. Most subjects were reinjecting before the effects of the previous MAP injection had lessened, resulting in multiple daily injections. The mean cumulative duration of MAP use before onset of MAP psychosis did not differ significantly between the 19 flashbackers (mean ± SD, 15.8 ± 21.0 months) and the 20 non-flashbackers (22.0 ± 32.1 months). The duration of the 23 user controls (32.8 ± 38.8 months) was significantly longer than in the 19 flashbackers ($Zc = 2.24$, $p < 0.05$) and the 8 subjects with persistent MAP psychosis ($Zc = 2.85$, $p < 0.01$). Flashbacks occurred following a period of normalcy of 6 to 730 days (114.9 ± 152.1 days) after the resolution of a previous MAP psy-

Table 1 Incidence of psychotic symptoms in the 19 flashbackers during flashbacks and previous MAP use, the 20 non-flashbackers and the 8 subjects with persistent MAP psychosis: The percentages do not total 100 because some subjects had more than one psychotic symptom

	Flashbackers				*Non-flashbackers*		*Subjects with persistent MAP psychosis*	
	During MAP psychosis n = 19 (%)		*During flashbacks n = 19 (%)*		*n = 20 (%)*		*n = 8 (%)*	
Auditory hallucinations	17	89.5	17	89.5	19	95.0	8	100.0
Comments or threats	13	68.4	17	89.5	12	60.0	8	100.0
Conversations	1	5.3	1	5.3	1	5.0	3	37.5
Elementary auditory hallucinations	6	31.6	7	36.8	6	30.0	4	50.0
Visual hallucinations	9	47.4	1	21.1	3	15.0	7	87.5
Scenes	0	0.0	7	10.5	1	5.0	2	25.0
Elementary visual hallucinations	3	15.8	4	21.1	0	0.0	2	25.0
Tactile hallucinations	1	5.3	0	0.0	0	0.0	0	0.0
Delusions of being watched	5	26.3	5	26.3	5	20.0	5	62.5
Delusions of being pursued	8	42.1	5	26.3	4	35.0	4	50.0
Delusions with murderous content	2	10.5	2	10.5	2	10.0	2	25.0
Delusions of reference	5	26.3	15	78.9	4	20.0	6	75.0
Thought broadcasting	3	15.8	4	21.1	4	20.0	4	50.0

Table 2 Stressful experiences during previous MAP use: percentages in fear-related psychotic symptoms do not total 100 since some subjects had more than one symptom. Values marked with the letters a and b are significantly different from the non-flashbackers, with $p<0.05$ and $p<0.01$ respectively (X^2tests).

	Flashbacker	*Subgroups*		*Subjects with persistent MAP psychosis*	*Non-flashbackers*
	n = 19 (%)	*A single episode n = 11 (%)*	*Subsequent episodes n = 8 (%)*	*n = 8 (%)*	*n = 20 (%)*
Stressful events	13 (68.4)[b]	8 (72.7)[b]	5 (62.5)[a]	5 (62.5)[a]	2 (10.0)
Physical abuse	8 (42.1)	4 (36.4)	4 (50.0)	4 (50.0)	2 (10.0)
Sexual abuse	1 (5.3)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Divorce	2 (10.5)	2 (18.2)[a]	0 (0.0)	0 (0.0)	0 (0.0)
Rejecting parents	1 (5.3)	1 (9.1)	0 (0.0)	1 (12.5)	0 (0.0)
Unwanted pregnancy	1 (5.3)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
DSM-III-R axis IV scores	3.63 ± 1.72[b]	3.73 ± 1.62[b]	3.50 ± 2.07[a]	3.38 ± 2.00[b]	1.40 ± 1.52
Fear-related symptoms	13 (68.4)[b]	7 (63.6)[b]	6 (75.0)[b]	3 (37.5)[a]	1 (5.0)
Threatening auditory hallucinations	7 (36.8)[b]	4 (36.4)[b]	3 (37.5)[b]	2 (25.0)	0 (0.0)
Threatening visual hallucinations	5 (26.3)[a]	2 (18.2)[a]	3 (37.5)[b]	1 (12.5)	0 (0.0)
Dead body or ghost	2 (5.3)	1 (9.1)	1 (12.5)	1 (12.5)	0 (0.0)
Blood-soaked face	2 (5.3)	1 (9.1)	1 (12.5)	0 (0.0)	0 (0.0)
Graveyard or blood	2 (5.3)	1 (9.1)	1 (12.5)	0 (0.0)	0 (0.0)
Delusions of being killed	2 (5.3)	0 (0.0)	2 (25.0)[a]	2 (25.0)[a]	0 (0.0)
Delusions of being pursued	9 (47.4)[a]	5 (45.5)[a]	4 (50.0)[a]	2 (25.0)	1 (5.0)

chosis, during which the flashbackers had abstained from MAP or other substances. The 19 flashbackers exhibited reactivated MAP psychosis without reexperiencing the original stressful events or the symptoms of PTSD or acute stress disorder as listed in the DSM-IV criteria. Consistent with previous reports [5], Schneider's first-rank symptoms (mainly positive symptoms) such as auditory hallucinations commenting or threatening on one's action, visual hallucinations, paranoid delusions, and thought broadcasting were most commonly found during MAP psychosis and flashbacks. The incidence of psychotic symptoms during flashbacks was not significantly different from that of the previous MAP psychosis ($X^2 = 11.09$, $df = 13$, $p = 0.60$, see Table **1**). During flashbacks, subjects continued to experience paranoid delusions in which they developed transient auditory and visual hallucinations. Auditory hallucinations lasted for 2 – 10 minutes and occurred 1 to 3 hours daily or up to 3 to 5 times a day. Visual hallucinations occurred sporadically from a few times weekly to daily. Paranoid delusions abated after 3 – 229 days. Thus, the total duration of flashbacks was 3 – 229 days (median, 50.0 days; mean ± SD, 62.2 ± 57.5 days).

Stressful experiences

As shown in Table **2**, the 19 flashbackers had been exposed to significantly higher numbers of stressful events ($X^2 = 6.46$, df = 1) and MAP-induced fear-related paranoid-hallucinatory states ($X^2 = 8.39$, df = 1) during previous MAP use than the 20 non-flashbackers. These events corresponded to severe or extreme types of psychosocial stressor (severe types: divorce, rejecting parents or unwanted pregnancy, with axis IV scores of 4; extreme types: physical and sexual abuse by a companion in drug use, with axis IV scores of 5). All these events had overwhelmingly threatened the subjects. The 6 flashbackers with no history of stressful events had experienced fear-related psychotic symptoms. Thus, compared with the 20 non-flashbackers, all flashbackers had been exposed to frightening, stressful experiences during previous MAP use. The numbers of stressful events and fear-related symptoms, and the axis IV scores in each of the 11 flashbackers with a single episode (stressful events, $X^2 = 6.03$, df = 1; fear-related symptoms $X^2 = 6.92$, df = 1; axis IV score Z = 3.75) and in the 8 flashbackers with subsequent episodes (stressful events $X^2 = 4.41$, df = 1; fear-related symptoms $X^2 = 7.62$, df = 1; axis IV score Z = 2.50) were significantly higher than for the 20 non-flashbackers. No score differed significantly between these two flashbackers subgroups. All 8 subjects with persistent MAP psychosis had experienced significantly higher numbers of threatening, stressful events ($X^2 = 4.41$, df = 1) and/or fear-related psychotic symptoms ($X^2 = 5.22$, df = 1) during previous MAP use than the 20 non-flashbackers. The axis IV scores in the 19 flashbackers (Z = 3.76) and in the 8 subjects with persistent MAP psychosis (Zc = 2.82) were significantly higher than for the 20 non-flashbackers. The factors triggering the flashbacks met the DSM-III-R criteria for a mild type of psychosocial stressor (axis IV scores of 2), involving mainly mild fear of other people; conflicts or confrontations with inmates, 35.7%; fear of emitting body odor, 10.7%; fear of prison setting involving fear of the prison staff, 39.3%; fear of other inmates' words and actions, 14.3%. Other factors were worry about family (3.6%), sleep disturbance due to tension (3.6%), and abdominal pain (3.6%). These factors represent non-specific psychosocial stressors that arise in general conflicts in the prison. The STAI-state scores did not differ significantly among the subject subgroups (H = 2.42, df = 4, p = 0.65): the flashbackers during flashbacks, 56.9 ± 9.2; the flashbackers at remission, 53.6 ± 11.7; the non-flashbackers, 53.2 ± 7.6; the user controls, 50.7 ± 5.6; the non-user controls, 53.3 ± 10.6. Neither blood pressure nor heart rate increased during flashbacks.

Plasma monoamine metabolite levels

As shown in Table **3**, repeated-measures ANOVA indicates a significant difference between flashbacks and remission in plasma NE levels (F(1,17) = 4.66). There was no evidence of interaction between the testing time (during flashbacks and remission) and neuroleptic treatment or its effect for plasma levels of any monoamine metabolite. Plasma NE levels during flashbacks in the 19 flashbackers were significantly higher than during remission, and were significantly higher than in the 20 non-flashbackers and the 23 user and 11 non-user controls. Plasma NE levels in the 8 subjects with persistent MAP psychosis were significantly higher than the 23 use and 11 non-user controls. Plasma 3-MT levels during flashbacks were significantly higher than during remission, and were significantly higher than in the 23 user controls. Plasma E levels did not differ significantly among the subject subgroups.

Among the 19 flashbackers, the 11 with a single episode had significantly higher NE levels during flashbacks than the 23 user controls, but their NE levels during flashbacks did not differ significantly from levels during remission. However, the 8 flashbackers with subsequent episodes had significantly higher NE levels during flashbacks than during remission, and significantly higher NE levels than the 20 non-flashbackers and the 23 user and 11 non-user controls. The two flashbacker subgroups had significantly higher 3-MT levels during flashbacks than the user controls.

During flashbacks, both the 6 medicated and the 13 later-medicated flashbackers had significantly higher NE levels during flashbacks than the 23 user and 11 non-user controls. The 13 later-medicated flashbackers had significantly higher 3-MT levels during flashbacks than the 6 medicated flashbackers and the 23 user controls.

Discussion

The MAP psychosis reported here differs from schizophrenia – schizophrenic thought disorder is characterized by a concreteness of abstract thought and an impairment in goal-directed thought [5, 40]. Reduction of functioning is not prominent in MAP psychosis. The 19 flashbackers had experienced paranoid-hallucinatory states after taking MAP, but not after exposure to any severe stressor. They exhibited transient paranoid-hallucinatory states closely resembling their previous MAP psychosis when exposed to subsequent mild stressors. Thus, the flashbackers did not meet the DSM-IV criteria for delusional disorder or brief psychotic disorders. There was no possibility for the secret use of MAP or other substances. The flashbacks therefore most likely occurred as a spontaneous psychosis due to previous MAP psychosis. Although psychedelic drug flashbacks are considered to be the transient reliving of a drug's effects, subjects continued to experience psychedelic drug flashbacks for 1 – 2 years in 82% of a group of 87 subjects [27], for 1.5 to 4 years in 66% of 53 subjects [18] or even for 5 years or more in some subjects described in DSM IV. Thus, the total duration of flashbacks including persistent paranoid delusions and one or more transient hallucinatory flashback episodes may not be very long for flashback phenomena. Posttraumatic flashbacks involving visual and auditory hallucinations precipitated by stress are a cardinal manifestation of PTSD according to the DSM-IV. Posttraumatic flashbacks are reexperiencing of a traumatic event in the form of flashbulb memories such as visual, olfactory, affective, auditory or kinesthetic imprints [46]. Our flashbackers exhibited a reactivated MAP psychosis without reexperiencing the original frightening, stressful events and the symptoms of PTSD such as hypervigilance, hyperarousal and avoidance as listed in DSM-IV criteria. They never remembered frightening, stressful experiences in the form of somatosensory flashback experiences, and all had narrative memories of these experiences. Such a memory-modulating effect of stressful experiences may reflect relatively prolonged paranoid-hallucinatory flashbacks in contrast to the brevity of PTSD flashbacks. Collectively, the flashbacks reported here did not meet DSM IV criteria for PTSD.

Table 3 Plasma levels of monoamine metabolites. Data are means (SD) pmol/ml. All monoaminergic values were square-root transformed to reduce skew. Values marked with the letter a-i indicate significant differences among the subject subgroups: [a] $p<0.05$ compared to the flashbackers during remission (repeated-measures ANOVA); [b] $p<0.05$ compared to the flashbackers during remission; [c] $p<0.05$; [d] $p<0.01$ compared to the non-flashbackers; [e] $p<0.05$, [f] $p<0.01$ compared to the user control; [g] $p<0.05$, [h] $p<0.01$ compared to the non-user controls; [i] $p<0.05$ compared to the medicated flashbackers (post hoc test).

Subject subgroups	*n*	*Age (years)*	*NE*	*E*
Flashbackers during flashbacks	19	27.9 ± 5.9	0.65 ± 0.68[a, b, c, f, h]	0.39 ± 0.55
Flashbackers with a single episode	11	28.4 ± 6.8	0.45 ± 0.64[e]	0.40 ± 0.56
Flashbackers with subsequent episodes	8	27.3 ± 4.9	0.93 ± 0.67[b, d, f, h]	0.39 ± 0.58
Medicated flashbackers	6	26.0 ± 2.2	0.67 ± 0.95[f, g]	0.14 ± 0.29
Later-medicated flashbackers	13	28.8 ± 7.0	0.64 ± 0.57[f, h]	0.57 ± 0.62
Flashbackers during remission	19	28.1 ± 6.2	0.34 ± 0.42	0.38 ± 0.58
Flashbackers with a single episode	11	28.6 ± 7.1	0.22 ± 0.26	0.21 ± 0.42
Flashbackers with subsequent episodes	8	27.3 ± 4.9	0.51 ± 0.54	0.60 ± 0.71
Medicated flashbackers	6	26.0 ± 2.2	0.43 ± 0.57	0.43 ± 0.57
Later-medicated flashbackers	13	29.0 ± 7.2	0.30 ± 0.35	0.35 ± 0.60
Subjects with persistent MAP psychosis	8	25.5 ± 2.5	0.56 ± 0.46[e, g]	0.49 ± 0.86
Non-flashbackers	20	30.5 ± 9.2	0.36 ± 0.35	0.72 ± 1.30
User controls	23	32.3 ± 8.4	0.15 ± 0.23	0.84 ± 1.67
Non-user controls	11	30.8 ± 6.1	0.17 ± 0.15	0.38 ± 0.44
		3.MT	DOPAC	DA
Flashbackers during flashbacks		1.33 ± 2.28[b, e]	0.14 ± 0.47	0.05 ± 0.09
Flashbackers with a single episode		1.28 ± 2.17[e]	0.22 ± 0.62	0.04 ± 0.08
Flashbackers with subsequent episodes		1.39 ± 2.58[e]	0.32 ± 0.01	0.08 ± 0.11
Medicated flashbackers		0.00 ± 0.00	0.01 ± 0.03	0.08 ± 0.09
Later-medicated flashbackers		1.94 ± 2.55[i]	0.20 ± 0.57	0.04 ± 0.09
Flashbackers during remission		0.33 ± 0.77	0.30 ± 0.62	0.11 ± 0.18
Flashbackers with a single episode		0.06 ± 0.19	0.23 ± 0.61	0.11 ± 0.17
Flashbackers with subsequent episodes		0.70 ± 1.10	0.40 ± 0.67	0.13 ± 0.21
Medicated flashbackers		0.12 ± 0.30	0.14 ± 0.20	0.04 ± 0.05
Later-medicated flashbackers		0.42 ± 0.91	0.37 ± 0.73	0.15 ± 0.21
Subjects with persistent MAP psychosis		0.45 ± 0.93	0.03 ± 0.09	0.13 ± 0.22
Non-flashbackers		0.93 ± 2.05	0.34 ± 0.63	0.14 ± 0.21
User controls		0.11 ± 0.41	0.19 ± 0.58	0.11 ± 0.19
Non-user controls		1.06 ± 1.76	0.42 ± 1.12	0.28 ± 0.25

Noradrenergic hyperactivity has been implicated in the mechanisms by which traumatic memories remain indelible for decades and are easily reawaked after exposure to residual traumatic memories [7,41]. In this respect, flashbacks due to previous MAP psychosis and PTSD may, in part, share mechanisms such as noradrenergic hyperreactivity to mild stress. Paranoid-hallucinatory or schizophreniform psychoses [43], and schizophreniform with paranoid features and depressive symptoms such as postictal psychosis [2] may occur in some of patients with epilepsy and in subjects after surgical treatment of temporal lobe epilepsy, respectively. None of the subjects had epilepsy. MAP-induced paranoid-hallucinatory states and related flashbacks did not meet DSM-IV criteria for schizophreniform disorders (such as disorganized speech or behavior, catatonic behavior, or negative symptoms). Paranoid-hallucinatory states in this study are not therefore related to any epileptic seizure.

The 19 flashbackers had been exposed to threatening stressful events, fear-related psychotic symptoms, or both during previous MAP use. They then exhibited flashbacks due to previous MAP psychosis in situations of mild psychosocial stressors, involving mainly mild fear of other people. Although plasma monoamine metabolite levels do not accurately reflect central monoamine neurotransmitter function, plasma levels of NE [38] and 3-MT [21] respectively reflect gross changes in whole brain's noradrenergic and dopaminergic metabolism. The plasma NE levels reported here were within or not excessively below normal Japanese values (0.04 – 0.4 ng/ml, 0.237 – 2.37 pmol/ml) [32]. Plasma 3-MT levels in this study were not outside the range of levels found in several healthy Japanese subjects (1.3 – 2.9 pmol/ml) [50]. The present findings suggest that increased peripheral noradrenergic activity is related to the occurrence of flashbacks. In animal studies, initial exposure to stressful stimuli resulted in sensitization of brain and peripheral noradrenergic systems to subsequent stress mild enough to have no measurable effect on non-exposed animals. It follows that re-exposure to similar but less severe stress can easily increase NE turnover and peripheral and brain NE levels [3,19]. AMPs induce enduring sensitization to stress via dopaminergic changes in the brain [37]. Overall, frightening stressful experiences, together with MAP use, may increase noradrenergic hyperreactivity to less severe situations (mainly mild fear of other people) than previous

similar situations (frightening stressful experiences), so that mild psychosocial stressors readily increase plasma NE levels. In this context, noradrenergic hyperactivity in response to mild psychosocial stressors may be causally related to the occurrence of flashbacks, rather than being the result of flashbacks. The 8 subjects with persistent MAP psychosis had been exposed to frightening psychotic symptoms as well as threatening stressful events during previous MAP use, and were then suffering from persisting MAP psychosis with elevated NE levels. Thus, noradrenergic hyperactivity may be related to persistent recurrences of MAP psychosis in situations of omnipresent, mild psychosocial stressors in the prison.

Brain 3-MT levels are a well-documented index of DA release that are more sensitive than homovanillic acid (HVA) or DOPAC [16,52]. In rats, administration of Benzedrine, a peripheral decarboxylase inhibitor, results in simultaneous synthesis of 3-MT in plasma, cerebrospinal fluid and the brain [21]. A peripheral origin of 3-MT can be postulated [11], even though 3-MT is metabolized from DA in central dopaminergic nerve terminals [52]. These findings suggest that there is an important correlation between 3-MT levels in plasma and brain. Thus, higher 3-MT levels during flashbacks may reflect increased DA release. It has been reported that repeated stressful stimuli sensitize 3-MT release under subsequent stress in rat brain [10]. Overall, frightening stressful experiences, together with MAP use, may induce increased sensitivity to stress associated with noradrenergic hyperactivity, and increased DA release in response to mild psychosocial stressors. This increased sensitivity may predispose to the occurrence of flashbacks and further episodes. These findings strengthen our previous studies indicating that noradrenergic hyperactivity, including increased DA release, is critical for the development of flashbacks [53 – 55]. Sensitization to stress, acting through noradrenergic systems, can induce recall of traumatic events [7]. By reproducing noradrenergic hyperactivity, memories of frightening and traumatic experiences can be elicited following exposure to stress related to the original trauma [41]. AMP-induced sensitization to stress in dopaminergic systems may be related to the enduring hypersensitivity to psychotogenic effects of stress found in spontaneous recurrences of AMP psychosis [37]. These observations suggest that noradrenergic hyperactivity and increased DA release could elicit memories of MAP psychosis related closely to frightening, stressful experiences in response to mild fear of other people. Mild psychosocial stressors then trigger flashbacks, including increased NE and 3-MT levels.

Plasma NE and 3-MT levels in the two flashbacker subgroups may be related to the significantly higher numbers of stressful events or fear-related symptoms found in these subgroups, compared to the 20 non-flashbackers. During flashbacks, the 11 flashbackers with subsequent episodes showed a much greater increase in NE levels, while the 8 flashbackers with a single episode had a lower increase. Both subgroups had slightly increased 3-MT levels during flashbacks. Noradrenergic hyperactivity is associated with psychotic relapse in schizophrenia [48]. Central and peripheral noradrenergic hyperreactivity to mild stress may be a precipitating factor in stress-related psychiatric disorders [3,19]. Overall, it is possible that noradrenergic hyperreactivity to mild stress induces susceptibility to psychotic decompensation. Thus, robust noradrenergic hyperactivity with slightly increased DA release in response to mild psychosocial stressors in flashbackers with subsequent episodes may be able to trigger the initial episode and further predispose to subsequent flashbacks. By contrast, less robust noradrenergic hyperactivity, with slightly increased DA release in response to mild psychosocial stressors, in flashbackers with a single episode may be insufficient for a predisposition to subsequent flashbacks. Robust noradrenergic hyperactivity with slightly increased DA release could therefore predict further episodes. This extends our earlier findings [53 – 55], and has practical implications in recurrent invasive psychotic states.

In view of recent drug-induced models (such as hallucinogen-induced states) of schizophrenia [13], the appropriateness of flashbacks as a vulnerability/stress model of schizophrenia demands reappraisal. Several lines of evidence suggest that chronic AMP effects and schizophrenia overlap in the neurobiology of idiopathic and drug-induced psychoses, by augmenting dopaminergic neurotransmission within the central nervous system [24]. Some subjects with schizophrenia exhibit emergence or worsening of their positive symptoms (e.g., paranoid-hallucinatory states) with increased DA release, following acute exposure to AMP at lower doses that induce no psychotic symptoms in healthy subjects [25]. Most schizophrenics have enduring hypersensitivity to aversive stimuli, which may be linked to relapses [44] in response to psychological stressors [25,30]. Moreover, schizophrenia might be associated with chronic recurrence of intermittent sensitized states of DA systems [23,30]. Collectively, a confluence of clinical and preclinical data implicates stress-sensitive systems in the pathophysiology of schizophrenia [23,25,30]. In this respect, neurochemical sensitization of central DA systems [25,54] or endogenous sensitization [23] has been proposed as a key step in the progression from vulnerability to an overt symptomatology. Progressive neurochemical sensitization, which may be due to aversive stimuli during early brain development, occurs with increased DA release when the capacity to compensate for perturbation in neural activity is diminished in situations of stressful experiences. This process may underlie the onset and relapse of illness [23,25,54]. Likewise, stress sensitization possibly induced by previous exposure to stressful experiences during previous MAP use may be responsible for the onset of the flashbacks due to previous MAP psychosis and further recurrences. Spontaneous recurrences of MAP psychosis may overlap with schizophrenia in susceptibility to paranoid-hallucinatory states. Although the mesolimbic DA system is implicated in neurochemical sensitization, DA hyperactivity may play only a limited role in generating positive symptoms. This is because DA-mediated stimulation of D2 receptors explains only 30% of the variance in the positive symptom changes in response to AMP challenge, and patients in remission show no evidence of increased DA activity [20,23]. A discrete neurochemical deficit could therefore account for recurrent positive psychotic episodes [20,23]. In this regard, schizophrenics who showed enhancement in DA release and NE activity during neuroleptic treatment are likely to relapse soon alter neuroleptic withdrawal, suggesting that increased DA release and noradrenergic hyperactivity may be related to relapse prediction [47]. Subjects with a history of AMP or MAP abuse frequently exhibit recurrences of MAP psychosis in response to psychosocial stressors, even after a long period of abstinence, due to AMP- or MAP-induced long-term sensitization of dopaminergic systems [39].

Experimental studies of schizophrenia in animals have relied on the AMP or MAP model, in which repeated administration of AMP or MAP induces long-lasting behavioral sensitization to subsequent exposure to small doses of stimulants and environmental stressors [37]. This behavioral sensitization has been proposed as being analogous to neurochemical sensitization [25], and may be an animal model of schizophrenia [40], in particular predicting the relapse of paranoid schizophrenia [39]. In this study, stress sensitization associated with noradrenergic hyperactivity and increased DA release may have an important role in the development of flashbacks. Taking these considerations together, stress sensitization associated with noradrenergic hyperactivity and increased DA release in response to mild stressors as described here corresponds to the neurochemical or endogenous sensitization proposed by Lieberman et al [25] and by Laruelle [23] as the pathophysiology of schizophrenia. Flashbacks and schizophrenia may therefore share common underlying mechanisms of susceptibility to paranoid-hallucinatory states, such as stress sensitization, noradrenergic hyperactivity and enhanced DA release. Consequently, flashbacks can be an appropriate human model for the susceptibility to onset and relapse of paranoid-hallucinatory states in schizophrenia.

We now discuss methodological issues and limits in our study. First, the different triggering mechanisms for flashbacks should be noted. Normal subjects undergoing a variety of sensory deprivation regimens such as progressive bilateral hearing loss [4] and bilaterally worse vision and living alone [17] may develop auditory, and visual hallucinations, respectively. These hallucinations are usually recognized by the subjects as being unreal perceptions, as pseudohallucinations [4]. All flashbackers were incarcerated in a group under the supervision of prison staff, and had never undergone sensory deprivation regimens. Their auditory and visual hallucinations were percept-experienced with a similar quality to a true percept. Therefore, their auditory and visual hallucinations could not reflect sensory deprivation or isolation. Second, the elevated levels of NE [33] and 3-MT [10] might be due to heightened autonomic arousal related to stress or anxiety. However, plasma E levels, which reflect fluctuations in emotional stress [12], were not affected by the flashbacks. STAI-state scores, heart rate and blood pressure were likewise unaffected. A stimulus of sufficient intensity as indicated by the heart rate can activate peripheral noradrenergic systems [1]. Therefore, the elevated NE and 3-MT levels do not reflect heightened sympathetic activity. Third, plasma NE levels are increased by exercise through increased blood flow in working muscles [26]. The flashbackers did not appear agitated, and their motor activity was highly restricted during flashbacks. The elevated NE levels cannot be attributed to excessive motor activity. Fourth, the neuroleptics used may affect plasma NE and 3-MT levels. Haloperidol (5 – 10 mg/day or 10 – 20 mg/day) has been shown to decrease plasma NE levels over a 6 week course of treatment in schizophrenics [14]. Infusion of chlorpromazine (25 mg) reportedly decreases plasma NE levels [36]. Other clinical studies have demonstrated that treatment with haloperidol (4 mg/day) for 5 weeks [6], or administration of haloperidol (4 – 8 mg/day) or thioridazine (150 – 400 mg/day) for at least 10 days [45] has no significant effect on peripheral noradrenergic activity. Recent clinical studies have shown that treatment with haloperidol (3 – 20 mg/day) for at least one year [29], or with haloperidol (5 – 15 mg/day) for 3 weeks [8] does not alter plasma NE levels. On the other hand, treatment with chlorpromazine (400 – 2,000 mg/day) for 8 days has been reported to raise levels of plasma NE [9]. Comparative clinical studies of the effects of neuroleptics on plasma 3-MT levels are scarce. A preclinical study has reported that injection of haloperidol (0.5 mg/kg) or chlorpromazine (20 mg/kg) has no significant effect on brain 3-MT levels [51]. However, brain 3-MT levels increase after injecting haloperidol (0.5 – 1.0 mg/kg), chlorpromazine (2.3 or 14.0 mg/kg) or thioridazine (5 or 30 mg/kg) [52]. Chronic haloperidol treatment reduces brain 3-MT levels [49]. Thus, neuroleptic effects on plasma NE and brain 3-MT levels appear to change with subject selection criteria or design of study. In our study, repeated-measures ANOVA revealed no significant effect of neuroleptic treatment on plasma NE or 3-MT levels. Plasma NE levels during flashbacks in both medicated and later-medicated flashbackers were significantly higher than in user and non-user controls. Plasma 3-MT levels during flashbacks in the later-medicated flashbackers, before they had received the neuroleptics, were significantly higher than in the medicated flashbackers or the user controls. Overall, the elevated NE and 3-MT levels cannot be attributed to our neuroleptic treatment. Since our analysis of the differences between the subject subgroups included subjects with and without neuroleptics, influence of neuroleptics on plasma NE and 3-MT levels cannot definitively be ruled out. Further studies are needed to settle this question. Finally, our findings are based on only a retrospective study in females in a prison environment, and there were only small numbers of subjects within the flashbacker subgroups. Results must therefore be interpreted with caution.

In conclusion, frightening stressful experiences, together with MAP use, may greatly increase sensitivity to stress associated with noradrenergic hyperreactivity and increased DA release. This increased sensitivity may elicit memories of MAP psychosis closely related to frightening, stressful experiences in situation of mild stressors, leading to the occurrence of flashbacks. Robust noradrenergic hyperreactivity (with slightly increased DA release) to mild psychosocial stressors may engender susceptibility to subsequent flashbacks. Stress sensitivity associated with noradrenergic hyperactivity and increased DA release in response to mild psychosocial stressors may correspond to neurochemical sensitization to environmental stressors; this may be a key step in progressive vulnerability regarding psychotic symptoms in the pathophysiology of schizophrenia. Flashbacks may serve as an appropriate human model of susceptibility to paranoid-hallucinatory states in schizophrenia.

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